Cystic Kidney Diseases

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Plan

• Autosomal recessive polycystic kidney disease
• Autosomal dominant polycystic kidney disease
• Nephronophtisis
• Autosomal dominant tubulointerstitial kidney disease
• Renal cysts in syndromic disorders
• Simple cysts
• Screening algorithm
ARPKD

- severe hepatorenal fibrocystic disorder (nonobstructive dilatation of the kidney collecting ducts and malformation of the portobiliary system).
- estimated frequency of 1 in 20,000 live births
- diagnosed in utero or at birth and manifests as progressive renal insufficiency and portal hypertension
ARPKD

Fetal ultrasound: enlarged hyperchogenic kidney

Autopsy revealed kidneys measuring 90mm
ARPKD-Histology
ARPKD

- Renal phenotype: enlarged echogenic kidneys with loss of corticomedullary differentiation
- Oligohydroamnion → “Potter sequence” (characteristic dysmorphic facies, pulmonary hypoplasia and limb defects).
- Perinatal mortality 30% because of respiratory insufficiency
- If survive the first month, 1-year survival 92% to 95%
ARPKD

• More than 60% of neonates with pulmonary hypoplasia may survive; about 25% need postnatal dialysis.
• After 10 years, 60% require renal replacement therapy.
• Liver fibrosis is always found and cholangiodyplasia is common. The Caroli phenotype is seen in up to 80% with perinatal manifestation.
• Recurrent cholangitis and cirrhosis may require liver transplantation in about 10% of patients.
ARPKD

- Histology is characterized by defective remodeling of the ductal plate with intrahepatic duct dilatation and progressive portal tract fibrosis.
- Portal hypertension may cause gastroesophageal varices and hypersplenism.
- Splenomegaly, thrombocytopenia, leukopenia, and anemia → splenic dysfunction and predisposition to bacterial infections
- Extensive dilatations of intrahepatic and extrahepatic bile ducts → risk of ascending bacterial cholangitis.
ARPKD Genetics

- polycystic and hepatic disease gene 1 (PKHD1) that encodes fibrocystin-polyductin complex (FPC)
- FPC is expressed in primary cilia of kidney and bile duct epithelial cells
- PKHD1 - large gene (470 kb), 86 exons, with 67 exons included in the longest open-reading frame transcript
- A number of alternatively spliced transcripts; the exact function and clinical significance unknown???
Ciliopathy Proteins and Their Relationships to the Cilium–Centrosome Complex (CCC)

ARPKD Genetics

- 750 pathogenic PKHD1 mutations*
- 44% classified as missense mutations
- p.T36 M accounts for 10% of all mutations
- Biallelic truncating mutations severe phenotype (neonatal demise)
- Missense mutations milder phenotype

*http://www.humgen.rwth-aachen.de/
ARPKD treatment

- Ventilatory support
- Nephrectomy? (no guidelines!)
- Hypertension (ACE Inhibitors, AR blockers)
- Cholangitis should be considered in every ARPKD patient with unexplained fever
ADPKD

• Autosomal dominant polycystic kidney disease (ADPKD) is usually an adult-onset disorder
• Caused by mutation in PKD1 (80-85%) or PKD2 (15-20%)
• About 2% of ADPKD patients present with early clinical manifestations before age 15 years
• Rarely manifests as a neonatal disease within a typical ADPKD family
• Mechanism: Coinheritance of a hypomorph PKD1 allele in trans with an inactivating PKD1 allele
ADPKD

- PKD1 mutations can manifest as a phenocopy of ARPKD (severe neonatal disease with negative family history)
- Mechanism: Inheritance of two incompletely penetrant PKD1 alleles in *trans*
- Extrarenal manifestation: polycystic liver disease (mild), Cysts in other epithelial organs (seminal vesicles, pancreas, arachnoid membrane), diverticulosis, cardiac valve prolapse (25%), intracerebral aneurysms (8%).
- Children with early onset ADPKD and positive family history for aneurysms should have MRI screening after the age of 20.

*Vujic et al. J Am SOC Nephrol 2010; 21:1097-1102*
NEPHRONOPHTYSIS

• Autosomal recessive tubulointerstitial disorder
• Onset between 4 and 6 years (polydipsia, polyuria, concentration defect)
• Slowly progressive decline of GFR
• Normocytic anemia before the onset of renal insufficiency
• Growth retardation
• Infantile variant (NPHP2 or NPHP3 genes) in the first few months with rapid progression to ESRD
NEPHRONOPHTHISIS

• Normal sized kidneys or hypoplastic (nephromegaly in infantile form)
• Cysts can be observed at the corticomedullary junction
• Extrarenal manifestations 10% to 20%
• tapetoretinal degeneration (Senior-Loken syndrome).
• Congenital hepatic fibrosis (milder than in ARPKD)
NEPHRONOPHTYSISIS-GENETICS

- 19 causative genes (NPHP1-19)
- Homozygous deletions in the NPHP1 21%
- Causative genes are still unknown in 70%
- Oligogenic inheritance (2 mutations in a single NPHP gene and a third in an additional NPHP gene)
- Cost effective – targeted next generation sequencing of the panel of NPHP genes

GLOMERULOCYSTIC KIDNEY DISEASE

- Histology - cystic dilatation of Bowman’s space in the context of multiple clinical disorders
- Kidneys are echogenic, small, normal or enlarged
- Kidney cysts are not always evident on US
- Hyperuricemia and an autosomal dominant inheritance pattern may be present in patients with UMOD mutations.
AUTOSOMAL DOMINANT TUBULO-INTERSTITIAL KIDNEY DISEASE*

• autosomal dominant inheritance
• bland urinary sediment with minimal blood and protein
• pathologic changes of tubular and interstitial fibrosis
• slowly progressive chronic kidney disease.
• Cysts invariable present (macro, micro, single, not always medullary)
• Genetics: mutations in UMOD, MUC-1, REN, HNF1B

HNF1B-Related Kidney Disease

- Affected kidney, pancreas, liver, and genital tract
- Diabetes has been described in 58% of HNF1B mutation carriers (MODY5)
- Renal: hypoplastic GCKD, cystic renal dysplasia, oligomeganephronia, solitary kidney, horseshoe kidney, hyperuricemia, hypomagnesemia
## Renal Cysts in Syndromic Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Clinical</th>
<th>Renal</th>
<th>Gene</th>
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</thead>
<tbody>
<tr>
<td>Tuberous sclerosis complex</td>
<td>AD</td>
<td>Hypomelanotic macules, Angiofibromas, Ungual fibromas, Shagreen patch,</td>
<td>Polycystic kidney disease, Angiomyolipoma, Renal cell carcinoma</td>
<td>TSC1, TSC2</td>
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<td></td>
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<td>Multiple retinal hamartomas, Cortical dysplasias, Subependymal nodules,</td>
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<td>Subependymal giant cell, Astrocytoma, Cardiac rhabdomyoma, Angiomyolipomas</td>
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<td>Bardet Biedl syndrome</td>
<td>AR, Oligogenic</td>
<td>Renal anomalies, Rod-cone dystrophy, Polydactyly, Obesity, Learning</td>
<td>fetal lobulation, calyceal blunting, clubbing or diverticula, medullary and cortical</td>
<td>BBS1-19</td>
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<td></td>
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<td>disabilities, Hypogonadism in male</td>
<td>cyst</td>
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<td>Oro-facial-digital syndrome</td>
<td>X-linked dominant</td>
<td>Craniofacial and oral anomalies, malformations of the digits in the hand,</td>
<td>bilateral kidney cysts similar to autosomal dominant polycystic kidney disease.</td>
<td>OFD1</td>
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<td></td>
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<td>and CNS malformations.</td>
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<td>Joubert Syndrome</td>
<td>Autosomal recessive</td>
<td>Skeletal abnormalities including a narrow chest, limb shortening,</td>
<td>bilateral kidney cysts.</td>
<td>DYNC2H1, IFT80, TTC21 B, NEK1</td>
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<td></td>
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<td>brachydactyly, short stature, hypertension and renal insufficiency</td>
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<tr>
<td>Meckel Gruber syndrome</td>
<td>Autosomal recessive</td>
<td>Occipital encephalocele postaxial polydactyly, skeletal dysplasia,</td>
<td>enlarged kidneys with varying degrees of cyst formation</td>
<td>MKS1, TMEM216, TMEM67, CEP290,</td>
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<td>microphthalmia, genital anomalies, cleft lip and palate, heart defects.</td>
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<td>RPGRIP1L, C9ZD2A, NEHP3, TCTN2,</td>
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<td>B9D1, B9D2, TMEM231</td>
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<tr>
<td>Von Hippel Lindau syndrome</td>
<td>Autosomal dominant</td>
<td>Tumors develop in both kidneys, adrenal glands, pancreas, brain or spine,</td>
<td>bilateral kidney cysts and bilateral multifocal renal cell carcinoma.</td>
<td>VHL</td>
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<td>eyes, and inner ears.</td>
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**RENAL CYSTS IN SYNDROMIC DISORDERS**
TUBEROUS SCLEROSIS

Angiomyolipoma

Bilateral polycystic kidneys
Simple cysts

- rarely occur before age of 20
- prevalence of 7% to 10% in the general population
- typically 1 cm or less but increase slowly over time in 25% of cases
- Ultrasound-sharply defined with thin, smooth walls without internal debris or septae
- Potentially malignant: presence of calcification, septae, loculation, wall thickening, and increased density after dye injection
A 9 year old boy with incidental finding of a large simple cyst in the left kidney
Algorithm for screening infants/children with kidney cysts

Research Laboratory/Registry

www.renalgenes.org

Contact. Prof. F. Hildebrandt, Boston Children’s Hospital, Harvard Medical School

ARegPKD, a European ARPKD registry study
Contact: Kathrin Ebner, Email: kathrin.ebner@uk-koeln.de

ADPKiDs study (EDTA-ESPN)
Contact: adpkids@opbg.net